REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

1. Information Disclosure Statement.

The Office Action indicates that the references submitted with the previous Amendment were not considered because they were not provided together with an information disclosure statement and listing. However, such a statement and listing was provided with the Amendment, as reflected in the enclosed postcard showing its receipt.

For ease of reference, a duplicate copy of the information disclosure statement and listing filed on July 19, 2005 is enclosed herewith. A further supplemental information disclosure statement is also provided herein, together with two additional references discussed herein. Consideration of the references is therefore respectfully requested.

In addition, because the references submitted with Applicant's July 19, 2005 response to the previous Office Action could have been considered at that time, it is also requested that the finality of the present Office Action be withdrawn.

2. Rejection of Claims 1-8, 11-12 and 14-18 under 35 USC Section 112, First Paragraph (new matter).

A new objection is raised to the claims under Section 112, first paragraph, on the basis that the limitation introduced into the claims directing that a neurotrophic composition be provided to "two or more" delivery sites, rather than the "one or more" sites recited in the original claims, is new matter not supported by a written description in the Specification.

Applicant respectfully disagrees. With respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the *In re Wertheim* decision at 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a

range of "25%- 60%" and specific examples of "36%" and "50%." The rejection of a new claim reciting a narrower range "between 35% and 60%" as lacking written description because the "35%" value was not explicitly recited in the Specification was overturned on appeal, because "[i]f lack of literal support alone were enough to support a rejection under § 112, then the statement of *In re Lukach* . . . that "the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of § 112," is empty verbiage." (*In re Wertheim*, 541 F.2d at 265).

As in the present claims, the Wertheim claims at issue covered a range ("solids level of at least 35%"; *id.* at 258), whereas the specification disclosed a broader range ("concentrated . . . until a concentration of 25 to 60% solid matter is reached", *id.* at 262; internal quotation marks omitted). The CCPA held that the specification supported the claimed range, even though the precise range of the claim was not repeated verbatim in the specification, cautioning that it would "let form triumph over substance" if it allowed the written description requirement to eviscerate claims that are narrowed during prosecution, simply because the patent applicant broadly disclosed in the original patent application but then narrowed his claims during prosecution (*id.* at 263).

In the present application, the concept that "two or more" delivery sites will be utilized is clearly inherent in the disclosure, and would be immediately comprehended by one of ordinary skill in the art. With respect to the disclosure, Applicant notes that the original claims encompassed a range of "one or more" delivery sites. Therefore, as the "or more" upper range was disclosed in the original specification, the question is only whether the "or more" than one delivery site includes two.

Applicant respectfully submits that the concept of "one or more" delivery sites necessarily defines "more" as extending to one more site; i.e., "two or more" sites in total. Lest there be any question in this respect, the Specification clearly describes the preferred numbers of delivery sites as being "upwards of 10," with 5 or more sites being relatively typical (Paragraph 0017), an approach exemplified *in vivo* at Paragraph 0077.

As such, consistent with the holding of the CCPA in *In re Wertheim*, the numerical limitation of "two" delivery sites is described by the range of "one or more" delivery sites, including "upwards of 10" such sites, even though the phrase "two delivery sites" does not appear *in haec verba* in the Specification. Reconsideration and withdrawal of the objection under Section 112, first paragraph, to Claims 1-8, 11-12 and 14-18 is therefore respectfully requested.

Applicant further notes that the Office Action indicates that withdrawal of the "same invention" type double-patenting rejection based on his prior '058 Patent is dependent upon the "two or more" limitation of the amended claims, maintenance of the withdrawal made in the present Office Action is also respectfully requested.

3. Rejection of Claims 1-8, 11-12 and 14-18, as well as of Claims 17-18, under 35 USC Section 112, First Paragraph (enablement).

The prior enablement rejection of the claims has been partially withdrawn, but partially maintained on the basis that "applicant did not provide any arguments or evidence traversing the previous issues of rejection based on the unpredictability of methods of gene therapy, or the site of delivery." (Office Action at page 4).

Applicant respectfully disagrees. Both grounds of rejection were addressed at length (with respect to Claims 1-17) in the previous Amendment, at pages 6, 7 and 9-12. To summarize the arguments made, they are:

a. The issue of whether methods for practicing gene therapy generally, and in the context of the methods for therapy of neurodegenerative disease specifically, have been resolved in Applicant's favor (including in, for example, the '058 Patent cited for 'same invention' double patenting purposes), who is therefore entitled to have such decision given "full faith and credit" with respect to the present application. (See full discussion of the full faith and credit dictates of MPEP 2134 and 706.04 at page 6 and page 9, first paragraph, of the Specification).

b. The question of whether those of ordinary skill in the art are enabled to select delivery sites in the brain has also been resolved previously in Applicant's favor (see, e.g., the '058 Patent, the '306 Patent and U.S. Patent No. 6,815,431 [treatment of Parkinson's Disease]). Moreover, the Specification clearly directs the artisan to direct the neurotrophic compositions of the invention to regions of the brain which contain neurotropin-responsive neurons into adulthood (see Paragraph 0014), which include, in the brain, the cholinergic basal forebrain neurons, locus coeruleus neurons, entorhinal (cortical) neurons, and thalamic neurons. The identity and location of such neurons is well known to those of ordinary skill in the art (see, e.g., the citations referenced at page 7 of the previous Amendment), and therefore need not be exhaustively described in the Specification. Note that, in this respect, Claim 1 explicitly recites that the delivery sites chosen will be those that provide access to "neurotrophin-responsive neurons in the mammalian brain."

Further, as demonstrated in the Examples in the Specification and by the Declaration of Dr. Mark Tuszynski (submitted with Applicant's response of July 19, 2005), the invention may be practiced targeting different populations of neurons in different regions of the brain. These include, for example, cholinergic neurons in the basal forebrain (implicated in Alzheimer's Disease; see, e.g., Specification at 0066-0069 and 0073-0079, as well as the Tuszynski Declaration at paragraphs 22-29) and dopaminergic neurons in the substantia nigra (implicated in Parkinson's Disease).

Further in this respect, Applicant notes that the Office Action avers that "no evidence is disclosed if the humans [treated as indicated in his Declaration] used in said experiments had Alzheimer's disease or Parkinson's disease, what specific adeno-associated viral vectors neurotrophins were delivered and if the humans were so afflicted, what the efficacy of the treatment was." (Office Action, bridging paragraph from pages 4 to 5). Applicant respectfully disagrees.

The *Nature Medicine* article submitted with, and discussed in, Applicant's response of July 19, 2005 (at pages 9-11) confirms that in human clinical trials, responses to expression of exogenous neurotrophin introduced into the brain according to the invention (using an AAV vector encoding NGF also described at paragraph 0063 of the Specification) have been remarkable. For example, the rate of progression of Alzehimer's Disease in the first patient treated (with the *ex vivo* approach) is estimated to have been slowed by upwards of 51%, a heretofore unprecedented result in treatment of AD (see Tuszynski, *et al., Nat. Medicine,* 11:551-555, 2005, at 553, first column, enclosed). As stated in the Specification, "[t]hose of ordinary skill in the art will appreciate that while [certain of] the Examples illustrate an ex vivo application of the invention, the results achieved will [also] be accessible through in vivo delivery..." (Specification at paragraph 0061).

Human clinical trials of the *in vivo* practice of the invention are also enjoying promising, if preliminary, results. These results offer hope that the beneficial effects produced in patients participating in the *ex vivo* trials may be realized for a longer period of time among patients treated with the *in vivo* approach, which does not rely on the longevity of exogenous cell grafts (see, the *Chicago Tribune* article dated August 14, 2005, enclosed herewith, and the report dated September 23, 2005 in the *San Diego Union-Tribune*, also enclosed herewith).

The *Nature Medicine* paper also reports promising results from a trial for treating Parkinson's Disease using the invention, at 553, second column. These results are also producing promising "real world" improvements in the condition of human patients, as recently reported by the licensee of this application (see, enclosed study report dated September 21, 2005). Hence, it is clear that the practice of the invention, as enabled by the Specification, has clear therapeutic implications for use in humans.

It will be appreciated, of course, that such human studies, while incredibly promising, are not required to demonstrate that practice of the present invention has been fully enabled by the Specification. To the contrary, studies in relevant animal models are sufficient to this end. In that respect, however, the Office Action contends that "neither the specification nor the art of

record indicates that these models [described in the inventor's Declaration and in the Specification] were predictive of the efficacy of a gene therapy treatment method for Alzheimer's Disease or Parkinson's Disease in humans." Again, Applicant respectfully disagrees.

In the Tusynski Declaration at paragraph 5, the animal models utilized are described as modeling the "neurodegeneration experienced in Parkinson's Disease (PD) or Alzheimer's Disease (AD)." The Declaration further confirms that the animal model utilized in the AD experiments described "mimics loss of cholinergic neurons in AD" (paragraph 23), while the model utilized in the PD experiments mimics the loss of dopamine production, neuronal density and motor function experienced in PD (paragraph 8). The animal model for AD is also described in the Specification (at paragraphs 0057-0060 and 0066-0068). These models are well known in the art to be relevant to the disease states noted (see, e.g., References A1, A3 and A6 re modeling AD, and A35 re modeling PD). It is this neurodegeneration that is "ameliorated" according to Claims 17 and 18 by delivery of a therapeutic neurotrophin according to Claim 1.

In view of the foregoing, reconsideration and withdrawal of the rejections of both Claims 1-8, 11-12 and 14-18, including the separate rejection of Claims 17 and 18, is respectfully requested.

4. Double Patenting Rejections.

The Office Action indicates that the "same invention" type double patenting rejection based on US 6,683,050 has been withdrawn, but that the withdrawal was based on the inclusion of the claim limitations regarded as being "new matter" in the application. As discussed in paragraph 2 above, the limitations in question are not new matter. As such, Applicant assumes that the double patenting rejection shall remain withdrawn. In addition, the terminal disclaimer offered over the '050 Patent in the event that the double patenting rejection was restated as an obviousness-type rejection is now moot, and is therefore withdrawn.

Claims 1, 11, 12 and 13-15 are also rejected on the basis of obviousness-type double patenting in view of U.S. Patent 6,451,306. A terminal disclaimer with respect to the '306 Patent is submitted herewith. On acceptance of the disclaimer, reconsideration and withdrawal of the double patenting rejection is respectfully requested.

5. Rejection of Claims 1 and 2 under 35 USC Section 102(b)

Martinez-Serrano, et al., 1995 is cited as anticipating the invention of Claims 1 and 2. Applicant respectfully disagrees.

The Martinez-Serrano researchers were interested in the question of whether a neurological morphology would be maintained by CNS-derived donor cells containing an exogenous growth factor transgene, upon grafting into brain tissue (*J. Neurosci.*, 15: 5668-5680, at 5668, second column). To this end, an experimental protocol was adopted under which the a *single* cluster of donor cells were grafted into *healthy* brain tissue, and the morphology of the donor cells and host cells adjacent to the graft was studied (*id.*, at 5674, first column).

In a subsequent experiment, the grafts were placed, then a fimbria-fornix transaction performed in the same surgical procedure (*id.*, at 5674, second column, and at 5679, first column). On the control sides of the animals' brains, a lesion formed (resulting in a 30% reduction in cholinergic cells at the lesion site), while virtually no lesion formed on the treated sides (*id.*, at pages 5674-5675, bridging paragraph).

Thus, at the time of its publication (i.e., without the benefit of hindsight provided by the present disclosure) Martinez-Serrano would have only be understood by the ordinary artisan as indicating that (1) the neurological morphology of CNS derived donor cells would be maintained after transplantation into the brain without overgrowth (making them suitable choices for use in grafts); and (2) growth factor expressed by such cells could assist healthy cells in resisting degeneration after subsequent axotomy. Neither observation teaches or suggests that expressed growth factor could be therapeutically administered to reverse the effects of existing

degeneration among brain cells, nor does the paper encourage administration of growth factor directly into brain cells (as encompassed by the present claims).

To the contrary, Martinez-Serrano strongly *discourage* introducing exogenous growth factor into brain cells by any means. In particular, the authors note that "since the transgene is not targeted to endogenous cells of the host brain, but rather expressed in the implanted cells, this gene transfer approach should minimize any possible risk of interference with host brain functions" (page 5679, first column). Hence, Martinez-Serrano teach away from the *in vivo* practice of the claimed invention.

As to the implanted cells, the authors teach that "mature glial cells" should be used, wherein the cells themselves function as "cellular chimeras" in the CNS. In that respect, the cells are believed to "become structurally integrated with the surrounding host tissue" within a 1 to 1.5 mm distance from the implantation site (page 5678-5679, bridging paragraph). According to the authors, therefore, it is not the growth factor molecule which travels up to 1.5 mm to surrounding cells, but the vehicle by which the growth factor is provided; i.e., the neural donor cells.

Nothing in this disclosure offers any suggestion to the art that growth factor may be introduced to more than one delivery site much less, as now claimed, delivery sites up to 10 mm distance apart.

For all of the foregoing reasons, the work described in the Martinez-Serrano paper not only differs from the presently claimed invention, the paper teaches away from the invention, thereby providing the art with no motivation to arrive at it. Reconsideration and withdrawal of the rejection of Claims 1 and 2 under Section 102(b) based on the paper is therefore respectfully requested.

6. Rejection of Claims 1 and 16 under 35 USC Section 102(b)

The Office Action indicates that rejection of Claims 1 and 16 as anticipated by Schinstine, et al. has been withdrawn, but that the withdrawal was based on the inclusion of the claim limitations regarded as being "new matter" in the application. As discussed in paragraph 2 above, the limitations in question are not new matter. As such, Applicant assumes that the rejection based on Schinstine, et al. shall remain withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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